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Ethics of animal research[1]

By I. Anna S. Olsson, Paul Robinson & Peter Sandøe

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Introduction

> Antibiotics, anaesthetics, vaccines, insulin for diabetes, open heart surgery, kidney dialysis and transplants, treatments for asthma, leukaemia and high blood pressure... these are just some of the major medical advances that have depended on the use of animals in medical research and testing.
> Research Defence Society, 2008

In the quoted defence of animal-based research, a number of examples where experiments on animals have played a role in the development of vaccines and therapeutic treatments are listed. Most researchers, including the authors of this chapter, agree that research with animals has contributed to the development of life sciences and medicine over the last centuries. However, it is much more difficult to say with a reasonable degree of certainty what would have been achieved if animals had not been used.

It seems likely that animals will continue to play a central role in biological and biomedical research in the foreseeable future, much as they do today. Current practice can be summarized by saying that experimental animals are used for three main purposes: to develop pharmaceutical and other medical products; to advance fundamental research in the life sciences; and to test the safety of potentially toxic products and substances. A rough idea of the relative numbers of animals used in these ways (in western countries at least) is conveyed by recent data which indicate that, of the experimental animals used in the EU in 2005, more than 60% of animals were used in biomedical

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research and development and fundamental biology. Production and quality control of products represented 15 % of the total number and toxicological and other safety evaluation 8% of the total number of animals used. The remaining animal uses include teaching, disease diagnoses and other purposes.

Much of this experimental activity requires live animals to be used, and this is the primary source of ethical concern. Some animals are housed so that they have limited freedom. Some are subjected to distressing or painful interventions. Nearly all of them are killed. The overwhelming majority are mammals with highly developed nervous systems. Unlike human subjects, however, they cannot consent to their own participation. Nor, generally, will they benefit from that participation, even if their descendents might. While few of us would question the desirability of discovering new ways to prevent, alleviate or cure human and animal diseases, these realities surely confront animal researchers with a question: Are we, as human beings, morally justified in using animals as tools for biomedical research?

This question can be addressed at different levels of generality. In this chapter we begin by addressing the most general question: What are our Duties to Animals? The point of this question is to see use of animals for research as one of many ways in which animals are used or interfered with by humans. What becomes clear when the issue is addressed at this level of generality is that there is not a single ethical view regarding human duties to animals to which all can consent. Rather, there seem to be different ethical approaches which live side by side. To allow for discussions of these approaches in a more structured way, a bit of philosophy is introduced. Three so-called theories of animal ethics, contractarianism, utilitarianism and animal rights are introduced with the dual aim of allowing readers to understand different views in the debate and to make up their own minds.

In the following sections of the chapter, we focus on what can be done to uphold a high ethical standard when animals are used for experimentation. This part of the discussion is based on the assumption - not universally accepted - that it can sometimes be acceptable to use animals for research. We begin this part of the discussion by examining the moral significance of the species to which an experimental animal belongs. Discussions about the use of animals in research often gravitate toward questions about benefits and costs, and the next two sections reflect this. One discusses benefits, paying particular attention to scientific factors affecting experimental outcomes. The other looks at ways in which costs, in the form of harm to animals, can be minimized. The final section before the conclusion of the chapter focuses on the ethical evaluation and regulation of animal-based research. Here we ask who, in practice, is responsible for ensuring that animals are treated ethically by scientists, and we consider whether the regulatory mechanisms typically relied upon today can be improved.

What are our Duties to Animals?

In today's society there are obviously many different views about what one is entitled to do to animals. However, these views are often rather superficial. They are rarely thought through. The same person may, when asked, express strong views about the importance of good animal welfare, and at the same time buy cheap animal products in the supermarket, seemingly without showing concern about the living conditions of the animals whose eggs, milk or meat they are buying. Because of this superficiality – which in many ways is very convenient for getting along with one's life - it may be a problem just to be led by one's feelings when discussing what is right and wrong in our dealings with animals. Such feelings are often unstable or ambivalent, and the ambivalence encourages double standards. This, however, is both morally objectionable and logically indefensible.Furthermore, it is clear that at present, in the West, people are engaged in an increasingly serious debate about the rights and wrongs of animal use. However, it seems unlikely that professionals taking part in this debate will be able to communicate effectively if they merely push for their own intuitively-held beliefs. To be able to make themselves understood to people who hold different views, they must be able to understand the nature of their disagreement.

To get a deeper understanding of the underlying ethical views, we shall here turn to moral philosophy that distinguishes a number of types of ethical theory. In principle, any of these might underlie a person's views about the acceptable use of animals. Here, three prominent theoretical positions will be presented: contractarianism (e g Narveson 1983), utilitarianism (e g Singer 1993 but also Frey 2001) and the animal rights view (Regan 1983) . These have been selected because they have direct and obvious implications for the ongoing debate over the use of animals for research. (There are other views. To get a more comprehensive presentation, see Sandøe and Christiansen, 2008).

Contractarianism: One sometimes hears it said that animals are morally insignificant, or lack moral status. In the past, this attitude has been defended on the basis that animals do not reason about the world, or on the basis that animals do not use language. Contractarians are broadly sympathetic to this kind of thinking. They regard morality as a system of hypothetical contracts that we tacitly enter into with one another. Animals cannot enter into these contracts, or agreements, lacking the linguistic and intellectual skills to do so. Hence, animals are not bearers of rights and duties.

Within the contractarian approach, animals *are* afforded ethical protection, however. It is just that the protection is indirect. Many people care about animals. They care especially about animals they own, of course, but they also care about animal use in general. They are therefore, highly unlikely to go along with the idea that animals can be treated however one chooses to treat them. This means that the hypothetical contracts that underlie morality contain 'clauses' requiring certain animals, at least, to be treated in ways we tend to regard as fitting or acceptable. Animals, on this view, can be compared with plants, or features of the natural landscape; they have no inherent moral right to be treated in a certain way, but we happen to value them, and sometimes rely on them, so they enjoy a borrowed kind of moral status, or secondary moral protection (see Sandøe and Christiansen, 2008, ch 2)

The implications of contractarianism for animal research are as follows. To the extent that people care about the animals used in experiments, the tacit contracts that constitute morality will contain clauses affording some protection to those animals. The scientific community ought to act in ways that people in general would broadly agree to, or contract into. Clearly, most people care about cats and dogs more than they care about rats and mice.[2] For the contractarian, this means that causing suffering to the former is likely to be more ethically objectionable than causing suffering to the latter. Similarly, non-human primates will probably receive more protection than other animals, because their plight is of very considerable concern to many people.

Ordinarily, of course, 'contractors' in all walks of life depend heavily on their ability to provide what people want and avoid doing what people dislike. On the contractarian picture of animal ethics, commonplace observations like these apply in a very direct way to the animal research community. What matters are the feelings and beliefs of fellow humans on whose collaboration one depends to gain a licence to operate. On this approach, then, setting ethical limits to the use of animals for research is really about defining a publicly acceptable framework that allows humankind to harvest the potential benefits of animal-based research.

It is a key strength of this view that it has a built-in tendency to capture public attitudes to animal experimentation. Contractarianism ensures that animal ethics reflect the way people actually feel about various kinds of animal use. Unfortunately, this connection with human attitudes can also be cited as a weakness of the contractarian position. On a contractarian approach to animal experimentation, the plight of the animals themselves is not really the issue. Do animals matter *only* insofar as we happen to care about them? What if we stopped caring? Would that make it okay to do whatever one wants to an animal? The next view to be considered, utilitarianism, will, unlike contractarianism, give a negative answer to these two questions.

According to *utilitarianism*, morality has one basic rule: always act so as to maximize the well-being of those affected by your actions. In practice, of course, we will still have to follow simpler, every-day moral principles, such as: Do not lie; Keep your promises; Look after your children and parents; etc. Many of these moral principles that we apply in everyday life can, according to utilitarianism, be looked on as rules of thumb that enable us to serve the single basic principle to create the greatest possible amount of good. The good to be maximized, well-being, is usually defined in terms of enjoyment and the absence of suffering. It therefore requires sentience[3]. Many of the animals in our care are sentient, thus are the sort of beings which can be given or denied this sort of well-being. Many of these animals therefore have moral status.

For the utilitarian, all well-being matters in exactly the same way, whether it belongs to a concert pianist or a pregnant sow. In this sense, all sentient creatures, human and nonhuman, deserve equal moral consideration. There will be plenty of situations in which we can improve the well-being of

[2] See the discussion of what has been labelled the 'socio-zoological scale' below in the section 'Does Animal Species Matter?' Contractarian theory automatically aligns animal ethics with this scale—for example, by affording greater moral protection to pets than wild animals.
[3] We discuss sentience in more detail below in the section "Does Animal Species Matter?"

animals in our care at little cost to our own welfare. When these situations arise we have a moral obligation to attend to the animals' interests, because we have a moral obligation to act always in ways that maximize well-being. In this sense, animals make genuine moral demands on us.

On the utilitarian approach, then, ethical decisions require us to strike the most favourable balance of benefits and costs for all the sentient individuals affected by what we do. But doing the right thing, according to the utilitarian, is not only a matter of doing what is optimal. It is also essential to do something rather than nothing: if something can be done to increase well-being, we have a duty to do it. This utilitarian duty to act so as to always bring about improvements has important consequences for society.

In contemporary western society, we retain a general tendency to give ourselves priority over animals. A thoroughgoing utilitarian will regard this tendency as essentially wrong. However, the human-centred outlook is obviously well established, and in view of this, it may well be that, for the time being at least, any attempt to ensure that sentient animals are accorded the same status as human beings is bound to fail. This may be especially true when it comes to animals used as tools in research that may potentially save many human lives. It may be that the best a utilitarian can hope to achieve is higher levels of animal welfare within the current system.

In the case of laboratory animals a pragmatic utilitarian might be willing to apply something called the 'principle of the three Rs' which we discuss in detail below.[4] This principle requires researchers to *replace* existing live-animal experiments with alternatives, *reduce* the number of animals used, and *refine* methods so as to cause animals less suffering (Russell & Burch 1959). It is not hard to see that less invasive sampling techniques, improved housing systems and more precise models requiring fewer animals to be used are likely to be viewed as morally attractive developments within the utilitarian perspective.

In the ethical debate over animal research, the main conflict is usually between the pursuit of human benefits, on the one hand, and the animals' interest in avoiding suffering, on the other. Sometimes, however, the utilitarian will want to weigh not just animal interests against human interests, but the interests of different animals against each other. Obviously animal experiments can benefit animals as well as humans. In fact, many of the insights underlying modern veterinary medicine have been derived from experiments on animals. When a pet cat is vaccinated against feline leukaemia, it benefits from immunological research performed on other cats — although of course, the primary purpose of the research was the development of treatments for human diseases. In deciding whether an animal experiment is ethically justifiable, it is sometimes necessary, then, to take into account the benefits of the results to *animals* as well as any hoped for human gains. Both of these can be set against costs to animals whose interests are sacrificed in the experiment.

Utilitarianism, as described above, suggests that animal interests are best sacrificed where such sacrifice leads to the protection or satisfaction of vital human interests — as happens in much

[4] See the section 'Minimizing Harm'. Note that some advocates of contractarianism and animal rights might well agree with the utilitarian about the desirability of applying the Principle of the 3Rs.

biomedical research. But is that an acceptable view? A more radical utilitarianism might be worth exploring. Animal experimentation sometimes means sacrificing vital animal interests in continued life and the avoidance of abject suffering. Insisting firmly that human and animal interests deserve equal consideration, the utilitarian philosopher Peter Singer has concluded that the sacrifice of such vital animal interests is acceptable only where the benefits are extraordinarily important:

> …if a single experiment could cure a disease like leukemia, that experiment would be justifiable. But in actual life the benefits are always much, much more remote, and more often than not they are nonexistent
>
> (Singer 1975, p. 85)

It is evident, then, that a wide range of views are represented within the utilitarian approach. Some utilitarian observers accept animal experiments when there are no alternatives and as long as we do our utmost to prevent and alleviate animal suffering. Others, like Singer, setting the demand for human benefit higher, would prefer to see nearly all such experiments abolished. What all utilitarians agree on, however, is the methodological precept that ethical decisions in animal research require us to balance the harm we do to laboratory animals against the benefits we derive for humans and other animals. This precept — the notion that we can work out what is ethical by trading off one set of interests against another — is precisely what is denied by advocates of animal rights.

Animal Rights: In response to the problem just described, some theorists of animal ethics have developed the view that animals have rights. The main point of moral rights is to define boundaries that should not be crossed, under any circumstances (unless of course the holder of the right waives the right, but this is academic if we are talking about animal rights). Quite what animal rights are *rights*, needs to be clarified, but even without this clarification one can see the appeal of a rights theory. The attribution of rights to animals allows us to insist that some ways of treating animals are totally unacceptable; not unacceptable only if enough people disapprove or if the benefits secured are too small, but unacceptable, *period*.

What rights do animals have, on this view? A radical suggestion, but one that is not without supporters, is that every sentient animal has the right not to be treated merely as a ‘means to an end’. Sentient animals should not be used as instruments in the pursuit of human goals. In particular, they should not be killed for human purposes. They have a right not to be killed. The implications of this way of looking at matters are dramatic and far-reaching. Tom Regan (1989) and other adherents of the animal rights view have argued for wholesale abolition of animal-based research (and most other forms of animal use including the use of animals for food production). It matters not that an experiment will cause only minor harm to the animals it involves. It matters not that this experiment is of extraordinary importance to humanity at large. The only thing that matters is that every time an animal is used for an experiment it is treated as a mere means to an end. This being so, animal experimentation should cease.

It is possible to imagine a more *moderate* advocacy of the animal rights approach, however. The right not to be killed is regarded as basic by some proponents of animal rights. But one might be doubtful about this, partly because animals, maybe with the exception of great apes, have a much more limited perspective on the future than we have. What matters to animals is that, here and now, they are well off, whereas we have aspirations and worries that reach across our entire lives. In light of this, one might suggest that animals have something like a right to protection from suffering, or certain levels of suffering. It could then be argued that all animals should be protected from suffering of the kind covered by the right—for example, the kind of suffering involving intense or prolonged pain or distress that the animal cannot control. Although this is not the standard animal rights view, it preserves the key idea that there are absolute, non-negotiable limits to what can be done to animals.

An important idea related to animal rights is the principle of *fairness.* The key point here is that what matters is not only the sum of positive and negative consequences, as claimed by the utilitarian approach, but the *distribution* of these consequences between individuals. For example, when animals are used in research involving pain, it may be considered fair, and therefore better, that a larger number of animals suffer a small and bearable amount of pain than it is that a few animals suffer strong pain – even if the total sum of pain is assumed to be larger in the first case (Tannenbaum 1999).

It should be clear that the three perspectives outlined above are not, in any simple way at least, compatible. Contractarians, for example, will have a permissive attitude to most animal experiments, whereas advocates of animal rights will take a restrictive, and often an abolitionist, position. Even moderate forms of the animal rights view will, on some occasions, conflict with the utilitarian approach. To see this, consider an experiment that causes a great deal of suffering to the animals involved, but that is very likely to lead to significant benefits to many humans or animals. Moderate rights advocates will probably want to prohibit the experiment so that *that* level of suffering is not visited on the animals by us. By contrast, utilitarians may not object to the experiment, because they think that, on balance, the benefits will probably outweigh the suffering imposed on the animals.

The use of rats as models of arthritis might be a relevant illustration . This model is created using injection of collagen, a substance from bone joints that causes a form of autoimmune arthritis to develop. Attempts have been made to alleviate the pain of the rat with painkillers. However, since all available painkillers also, directly or indirectly, have anti-inflammatory effects, their use may lead to undesirable interference with the research. It seems then reasonable to expect that the rats used to test potential drugs for arthritis may suffer pain similar to that endured by human arthritis patients.

This kind of model would be accepted by the contractarian. The brutal truth is that in the potential contract negotiation, the animal has nothing to offer in return for not being experimented on .It could also be accepted from a utilitarian perspective, with the argument that the admittedly, rather high cost imposed on the animals is outweighed by potential benefits to arthritis patients. However,

from even a moderate rights perspective, the experiment may look unacceptable; even moderate animal rights place a non-negotiable duty on us not to cause the relatively high level of suffering associated with multiple inflammations in joints.

Where does this leave matters? It is important to see that to say that the three approaches we are considering do not agree upon the rights and wrongs of animal experimentation. So there is need for discussion. Even though society will define limits in terms of legislation, each person will have her or his limits for what is considered acceptable regarding animal use – including use of animals for research. And different persons will almost always have different limits. In light of the ethical theories presented above, it is not only possible to make up one's own mind about what is right and wrong in our dealings with animals, it is also possible to understand the views of other people. Such an understanding is an important requisite for a civilized dialogue about animal use.

One of the issues that may come up in such a dialogue concerns the choice of animal species to be used in experimentation. We will turn to this issue next.

Does Animal Species Matter?

Animals of very different species are used in research. The choice of animal depends heavily on the kind of research being done, of course, but it is also affected by the experience and expertise of the researcher, the facilities of the institution, legislation, and sometimes public discussion in the country where the work is being carried out. The significance of these last factors is brought out by the fact that, even in, for example, *in vivo* research in the neurosciences requiring an animal with complex enough nervous system to embody mechanisms for learning and memory formation, the available research species range from nematodes to chimpanzees.[5]

Does the choice of species matter when it comes to *ethical* evaluation of animal-based research? It does, as we will now try to explain, but just how it matters is determined differently by different ethical theories. Contractarians will be concerned primarily with public sensitivities to the experimental use of different species. Through their impact on the tacit contracts we live under, these differentiated sensitivities give rise to a species-specific ethics of animal use. By contrast, utilitarians will focus on the issue of whether animals of a particular species are capable of suffering or frustration. The more rigorously it can be demonstrated that animals of a given species are able to suffer or experience frustration, the stronger the case will be for not using them. Similarly, advocates of animal rights will be concerned mainly about psychological sophistication, since rights are more readily ascribed to animals with advanced mental capacities.

In ethical discussion of the significance of species, two concepts are especially important; that of *sentience* and that of the *socio-zoological scale*. We shall therefore organize what we have to say around these concepts.

Sentience is the capacity to perceive or feel things. A sentient creature experiences the world around it (e g Duncan 2006). It may also experience feelings and emotions. In the words of Thomas Nagel in his classical analysis of this type of conscious experience "the fact that an organism has conscious experience *at all* means, basically, that there is something it is like to *be* that organism" (Nagel 1974) . Scientific understanding of sentience (both human and animal) is still limited. Neurobiologists have not yet managed to explain it, in terms of the material mechanisms of the nervous system.

In general, our belief that other individuals are sentient is based on the observation that they are behaviourally and physically similar to us. In other words, if an individual acts in a way that is similar to the way we would act in a certain kind of circumstance and that individual possesses something like a central nervous system, we regard it as probable, on the basis of an argument from analogy, that this individual is sentient. This reasoning is relatively uncontroversial for adult human beings, but when we extend it to non-human animals the issues become more complicated. Here, verbal evidence is unavailable and the behavioural and physical similarities are more limited. Although common sense detects sentience in many species, the scientific case for attributing it obviously needs to be based on systematically assessed evidence.

Smith and Boyd (1991) set out a systematic method of assessment of the kind needed here. They provide a checklist of neuroanatomical/physiological and behavioural criteria that can be used to determine whether a non-human animal has the capacity for pain, stress and anxiety. In relation to any of these kinds of experience, the checklist will include the possession of higher brain centres and evidence of behavioural reaction to potentially nociceptive, anxiogenic or stressful experiences. Further evidence will accumulate if the behavioural reactions are modulated by drugs with a known anxiolytic or analgesic effect in humans. Evidence will also accrue if peripheral nervous structures (including receptors, signal substances and hormones) are involved in each type of reaction, especially if there is a connection between these latter structures and the higher brain centres. As an increasing number of these criteria are met, the case for categorizing the animal as sentient builds.

When we look at the way taxonomically distinct animals fare under systematic scrutiny of this kind, we see that there are two important lessons to be learned. The first, is that all vertebrates meet the criteria for sentience. When Smith and Boyd's original analysis was published, positive evidence existed only for mammals and birds, but over the last decade, it has been demonstrated that the criteria are also met by fish (Ashley & Sneddon 2008, Braithwaite & Boulcott 2008). The second lesson is that, for many of the invertebrates, we still know too little to be able to say whether sentience can safely be attributed. Thus, while Eisemann and colleagues (1984) have presented a list of reasons why it is unlikely that insects are able to feel pain (including their lack of a behavioural response to protect an injured limb). Lockwood (1987) and Sherwin (2001), relying primarily on behavioural evidence, have argued that we should consider extending the argument of analogy to support the conclusion that insects are sentient beings.

Ethically speaking, then, how important is sentience as a factor in the selection of species for animal research? In one way, it might be said to be very significant. Both utilitarians and advocates of

animal rights attach significance to it; and even the contractarian might have an indirect interest in it, since sentient animals tend to matter more to humans than non-sentient ones. In another way, however, the significance of sentience *as a criterion of species selection* can be seriously doubted. It is relatively poorly understood and it is attributed to animals largely on the basis of imperfect analogies. Worse, a systematic checklist of scientifically respectable indicators shows that sentience is possessed by all vertebrates and possibly some invertebrates. That is not of much help if one is trying to determine which species to use in a potentially painful *in vivo* procedure.

There is a rather different way to approach the questions of whether and how animal species matters. Throughout human culture, there is clearly a perception of *hierarchy* among animals—a quasi-moral ordering that gives some species higher status than others. This hierarchy has been labelled 'the socio-zoological scale' (Arluke & Sanders 1996). The central idea of the scale is that people rate animal species as morally more or less important, and therefore more or less worth protecting, on the basis of a number of factors. These include how useful an animal is, how closely people typically associate with it, and how 'cute' it is. They also include how dangerous the animal is capable of being and how 'demonic' it is perceived to be.

Clearly, the socio-zoological scale varies from place to place and time to time, but today at least, and in western societies, some companion animal species, notably dogs and cats, seem to be at the top of it. Among other animals, large carnivores and non-human primates also figure at the top end of the scale. In the middle are large farm animal species such as cattle and pigs. Towards the bottom are pests or vermin such as rats and mice. Fish, viewed by some to be alien, cold and slimy, also appear to be quite low down the scale. At any rate, among the animals used for research there is a hierarchy, running from primates at the top, to rodents and fish, and on down to insects and other invertebrates.

The socio-zoological scale is, in many ways, based on tradition and unexamined prejudice, and its use as a basis of animal protection can be criticized both scientifically and ethically. From the utilitarian and the animal rights perspective, it is bound to seem morally wrong to discriminate among animals solely on the basis of the scale—an unfairness comparable to racist treatment of humans. On the contractarian view, on the other hand, there is nothing problematic about treating animals in line with the scale, and thus giving more protection to primates and dogs than is given to rodents and fish. Indeed, this is a morally attractive policy. This is, because, on the contractarian view, animals matter only to the extent that they matter to humans.

We conclude this section with a case illustrating the complex way in which the socio-zoological scale and sentience, and contractarianism and utilitarianism, sometimes interact with one another. Looking for a vertebrate which is smaller and easier to reproduce and manipulate genetically than the typical laboratory rodent, life science researchers are increasingly turning to zebrafish. From the contractarian/socio-zoological perspective, the use of this species in research is relatively unproblematic. Fish look very different from us; plainly they live in conditions quite unlike those we live in; and their plight matters to the average person much less than that of the domestic cat or possibly even the laboratory rat. For the utilitarian, however, the fact that fish are sentient may

render their employment in research morally questionable. Certainly, from the utilitarian perspective, we will be obliged to consider the harm that research may do to the fish and make efforts to prevent it. Here, the perceived distance between human beings and fish may be a disadvantage for the fish, since it may make it difficult for a human observer to recognize the fish's signs of distress—particularly given our relative lack of knowledge of pain and fear behaviour in these animals.

How can Benefits be Maximized?

Broadly speaking, the aim of animal research is to secure benefits—chiefly through the acquisition of new knowledge that provides answers to fundamental questions in biology or improves human and animal health and safety. However, as many animal researchers will ruefully confirm from personal experience, the assumption that benefits will be delivered cannot be taken for granted. Science is not a predictable 'manufacturing' activity, and even when we are armed with well-defined questions and correctly designed and carefully executed experiments, it is sometimes impossible to predict whether a research project will improve our understanding of important biological mechanisms or lead to the development of therapeutics.

However difficult it is to predict them, assessing benefits is of course, fundamental for balancing them against the harm the experimental procedures may cause to the animals involved. Assessments of benefits also help to promote the most effective use of resources. Here it is important to say that assessing benefit is *not* a question of distinguishing between applied and fundamental research. Instead, the aim should be to address whether a suggested research project is likely to be able to generate the benefits it aims to. Drawing on data and feedback from European ethics review committees, the Federation of European Laboratory Animal Science Associations (FELASA) working group has recently described a set of key questions that ought to be asked about any research project involving animals (Smith et al. 2007). On the benefit side, these questions include:

* How will the results add to existing knowledge and how will they be used?
* Are the objectives realistic, original and timely?
* How is the work related to previous and ongoing work in the research group and elsewhere?
* How likely is it that the benefits will be attained, based on:

    - Choice of animal model and scientific approach
    - Experimental design
    - Competence of staff
    - Appropriate facilities
    - Communication of results

In academic research, the first two questions are typically addressed in the scientific evaluation of funding applications. We will focus here on the last question, and in particular, on issues connected with the choice of animal model, experimental design and communication.

In animal research, the suitability of *animal models* is often a critical factor determining whether or not the expected scientific and medical benefits are secured. In some areas of research, the choice of animal species to be used is obvious; the agricultural scientist interested in aspects of dairy cow metabolism will develop his research on dairy cows. But in much fundamental biology and biomedical research, animals are used as *models*: researchers study animals of one species with the aim of gaining understanding with a wider application, or with application to another species (typically humans).

Critical discussion of what characterizes a good animal model is curiously rare in the scientific literature. Most review papers on animal models limit themselves to an overview of the models and the connected discussion of any results that have been generated in studies using them. However, it has been forcefully pointed out that suitable animal models, and the appropriate use of them, are crucial in improving the success rate of pharmaceutical drug development, i.e. in moving from a promising compound to an approved, marketable drug (Kola and Landis, 2004; Markou et al 2009) .

Critical evaluations of animal models address various aspects of validity. The evaluative methods used have been developed most extensively in the field of neurobehaviour, following Paul Willner's (1984) enquiries into depression models. The most reliable measure of how well a model models is, of course, 'predictive validity', i.e. how well results obtained using the model predict outcomes in other species of interest. But it will often be many years before such information is available about a model. Thus, in the development of treatments for human disorders, such validity is confirmed only when putatively effective compounds have made it all the way into studies with human volunteers—a process normally taking at least ten years. Therefore, researchers will look for earlier theoretical indications of model validity. The notion of 'construct validity', recording how similar the underlying mechanisms of the model and the other species of interest are, is useful here .

Unavoidably, scientists operate under practical constraints. Most research is to some extent dependent on existing technologies. It is shaped by factors such as, what models have been used before, what models the researcher has expertise in, whether an animal colony has already been set up at high cost, and so on. A telling example here is provided by genetic models of Huntington's Disease. In a recent study, Heng and coworkers (2008 page 8) conclude that "The practical advantages of the strong R6/2 phenotype [with poorer construct validity] make it unlikely that it will be replaced as the preferred model […]The milder phenotype and late onset of behavioural abnormalities of transgenic full length and knock-in murine models [with better construct validity] make them difficult to use for preclinical pharmacology."

This kind of decision reflects the reality in which scientists operate. However, the simple, general aim should be to use the best scientific model for the study in question. As gene technology has developed over the last decades, there are now many transgenic models available for diseases of a genetic origin. Is it then still relevant to use the older, pharmacologically-induced models? This, and related, questions can be applied to a wide range of research areas.

We now move on to look at the way *experimental planning and design* affect research benefits, as this is an issue around which considerable and challenging evidence has accumulated over the last couple of years. We will use the example of animal research underlying the development of treatments for stroke in humans. In this field, a number of compounds have shown neuroprotective effects in animal models, but very few have turned out to be effective in clinical trials on humans (van der Worp et al. 2005). This could be explained by the fact that animals are poor stroke models for the human condition and offer low predictive validity. However, this is not the only plausible explanation. Researchers concerned over the limited translation of preclinical research results into effective human stroke treatments have carried out several systematic reviews of the earlier animal experiments. They have found a number of critical shortcomings in experimentalplanning and design.

In many of the animal experiments, for example, the efficacy of the prospective treatment was probably overestimated as a result of design bias. Often, animals were not randomly allocated to treatments; and researchers, who were not blinded when they administered treatments (drug or control) or assessed outcomes, may have influenced measurements unconsciously (van der Warp et al. 2005; Crossley et al 2008). Significant clinical differences were also an unwelcome factor, in that the animals used were generally young and healthy before the experimentally induced stroke, while human stroke patients are often elderly and hypertense (Macleod & Sandercock 2005).

The third issue we will discuss is *communication*. By and large, if research is to be beneficial, it will be important for the results to be made public. Publication in peer-reviewed journals is a prominent feature of modern academic life, particularly in the sciences. As is well known, the performance of today's researchers is measured largely on the basis of the number of publications they have in influential journals. Thus, at least in academia, there is no doubt that researchers will invest time and effort in the communication of their results. However, it is generally difficult to get studies with negative results (no effect of treatment) published. As a direct consequence of this, publications are likely to reflect only a subset of the research that has been carried out in the field.

This has serious ethical consequences. In particular, it affects the number of animals used in research, as is explained in the following passage: "the 'publication bias' of journals in favor of hypothesis-confirming results [...] might be a reason for the slow progress in the development of new animal models and their validation. Negative results often go unpublished, and poor concepts, hypotheses, and models survive, notwithstanding a vast amount of contradictory data, merely because these data are not made available to the scientific community [...]. Publication of negative findings from well-conceived and performed studies can help investigators to evaluate and ultimately abandon the development of an invalid and irrelevant animal model and help reduce the unnecessary use of laboratory animals" (Van der Staay 2006 page 147). It can be powerfully argued, then, that there is an urgent need to create a coordinated, internationally recognized, searchable database where data on negative experimental findings can be deposited.

To this point, we have focused exclusively on biomedical research, where the main purpose is to understand disease mechanisms and develop treatments. Where fundamental biological research is

concerned, the practical benefits of using animals tend to be harder to predict; as applications of any results are further away from the research itself. By and large, it is not a useful exercise to ask whether an applied biomedical study is more likely to deliver benefit than a fundamental study of biological mechanisms. The advance of science and technology requires both varieties of research to be pursued.

How can Harm be Minimized?

In discussing scientific benefits above, we pointed out that a balance of benefits and harms is struck in ethically-acceptable research. We now turn to the other side of this equation; the harm factor. Ethical concerns about compromised animal welfare are rarely addressed effectively via a demonstration of human benefit alone. Efforts to reduce the harm done to animals during the research are generally important as well. Indeed, in ethical terms, harm reduction may be the more urgent concern. Certain levels of pain and suffering imposed on animals in the name of science are regarded by most people today as quite literally intolerable—a belief readily understood in terms of moderate animals rights, of course. But if this is right, there will be certain kinds of experimental procedures in which animals are caused high levels of pain, for which no amount of reassurance about benefits will serve as justification. The only way to deal with these ethical concerns will be by mitigating the animal harm.

The 3Rs principle (Russell & Burch 1959) addresses harm reduction through three approaches: the *replacement* of animal research with alternative animal-free methods, the *reduction* of the number of animals used, and the *refinement* of methods to minimize the distress caused to animals used in research. In what follows, we shall examine each R in turn, seeking to bring out the main consequences for animal research ethics.

The *Replacement Principle* is particularly important from the ethical viewpoint, since it is one of the few ethical precepts over which there is broad consensus. It is, for example, the only element of the 3Rs animal rights advocates endorse. The idea behind it is simple: if it is possible to obtain scientific benefits without using live animals, we should do so.

Scientists reading this chapter will be aware that experimental procedures that do not involve live animals, such as *in vitro* (e.g. cell lines), *ex vivo* (e.g. tissue culture), and *in silico* (e.g. bioinformatics) methods, are widely used in research laboratories already . In fact, these methods and the techniques that employ animal research subjects often work in a complementary fashion. However, strictly speaking, replacement requires existing procedures using animals to be abandoned in favour of animal-free methods, and this kind of readjustment is rarely straightforward.

Typically, when they apply for ethical approval, scientists are asked to explain why their proposed studies cannot be carried out without animals. Typically, the answer given is that the study requires the complexity of a complete living organism and is therefore not suitable for *in vitro* approaches. Is it possible to challenge that answer? It may be difficult to do so today, but science is a rapidly

developing endeavour, and as new methods appear, the possibilities change. Procedures involving animals may come to be replaced by novel *in vitro* and *in silico* methods, or by carefully designed studies with human volunteers or innovative uses of existing patient data.

In biomedical research, new techniques are approaching, or even entering, a sphere of research activity traditionally dominated by animal models. In the early research phase, *in vitro* methods play an important role in characterizing potentially effective compounds prior to preclinical research on animals (e g Markou et al 2009). At a later stage, the pharmacokinetics of candidate drugs are normally studied in animals. However, microdosing techniques, in which the uptake and metabolism of a drug is studied in human volunteers given doses so low they have no biologically significant effect, are being explored (Rowland, 2006) .[6]

Innovative use of human data permitting animal replacement can be illustrated with two cases. Conventionally, the genetic effects and effects of the intrauterine environment on foetal origins of chronic disease are researched with embryo transfer or cross-fostering of animals. However, human medically-assisted reproduction also results in parent-offspring pairs with contrasting combinations of genetic and environmental similarity/dissimilarity. Exploiting this, a research team has recently used fertility clinic records to build a database of information that can be used to study the effects of maternally provided prenatal environment directly on human data (Thapar et al, 2007) . In a second case, a workshop bringing together scientists and promoters of alternatives to animal-based pain studies, concluded by listing studies using human volunteers that would not only decrease the number of animals used, but would also produce more useful data by allowing direct links to be established between the human subjective pain experience and the biological parameters under study (Langley et al, 2008) .

While the previous examples concern research, overall development of replacement methods has focused on routine testing, the production of biological material, and teaching. A steadily (albeit slowly) increasing number of alternative test methods have gained regulatory acceptance (ECVAM, 2008) and the highly invasive *in vivo* production of monoclonal antibodies, using the ascites method in mice, can, in most cases, now be avoided (Hendriksen 1998). A number of teaching tools, ranging from videos, to interactive software, to highly sophisticated mannequins allow living and euthanized animals to be replaced at various levels of teaching (Interniche, 2008). Through a combination of novel teaching tools and carefully guided practice on patients in the veterinary hospital, it is even possible to complete veterinary training without killing animals or performing invasive treatments on them, solely for training purposes (Knight 2007).

Let us turn to the *Reduction Principle*. In animal studies that involve harm, the use of fewer animals will normally cut (as it were) collective animal suffering. That is the primary ethical motivation for reduction.[7] However, reduction has other benefits. For one thing, it is good resource management; laboratory animals, and their housing and care, are costly and research resources are limited.

[6] This application of microdosing is yet to be fully validated.
[7] Even in animal studies that do *not* involve harm, reduction may still be thought valuable: an animal rights advocate, for example, might welcome the fact that fewer animals are being used as means to an end.

Reduction considerations may also go hand-in-hand with good (i.e. efficient) experimental design with proper attention paid to standardization and the control of variation (Nevalainen 2004), and the choice of administration routes with a high degree of control (Svendsen 2005).

It is important to appreciate, on the other hand, that reduction may have an adverse impact. It has been pointed out that using too few animals to produce meaningful results is as unethical as using more animals than necessary (Nevalainen, 2004) , and interestingly a number of systematic reviews indicate that many animal studies use too few animals to provide reliable data (Sena et al 2007) . Such studies cause harm without benefits and involve poor use of resources.

Another problem—essentially a conflict between reduction and refinement—arises because lowering the total number of animals used will sometimes place a greater burden on each animal that continues to be used. If a given quantity of plasma can be obtained by bleeding the same animal several times instead of bleeding several animals once, it is unclear, to say the least, whether we would be making the world a better place by doing the former (Hansen et al 1999). It is certainly not eccentric to suppose that, if a burden must be borne, it is best shared. This was presented above as the principle of fairness to the individual animal (Tannenbaum 1999) and is also a reason to think critically about the possibility of reducing animal numbers by re-use of animals. This does of course not mean that re-use of animals is not worth considering - as long as the accumulated burden on one animal is not larger than what is acceptable within a single procedure.

The notion of 'animal numbers' is also less clear than might initially be supposed. What are we to reduce? The total number of animals used? Or the number of animals used relative to scientific output? After a period of steady decline, figures on laboratory animal use have risen over the last few years (Hudson, 2007). However, growth in investment in biomedical research may mean that the number of animals now being used relative to the amount of scientific activity taking place is falling.[8]

Again, should we be concentrating on the number of animals being used or the number of animals *suffering*? Not all animal research induces pain or suffering. The majority of approved procedures in animals are classified as minimally invasive. In many experimental regimes, animals are euthanized before they are exposed to invasive treatment or develop signs of disease. Utilitarians will want to focus exclusively on the number of animals that suffer. Proponents of animal rights may prefer to talk about reductions in total numbers. So might contractarians, if public attitudes were to become fiercely animal liberationist.

Once it has been shown that a research aim cannot be pursued without animal use, and once the animal numbers have been cut as much as possible, the *Refinement Principle* urges us to minimize any pain or distress that will be caused by amending experimental procedures. Few people would challenge this principle—at least, so long as conformity with it poses no threat to scientific results and does not require exorbitant funding. The only thing we need note is that limits on refinement

[8] The figures visible to the public portray the absolute numbers of animals used–an issue of great relevance to those involved in public science outreach activities.

may be required by the fact, noted above, that an inverse relationship sometimes exists between refinement and reduction.

Experiments can be refined in various ways. We mention only a few. The most direct strategy is to adapt experimental procedures so that they cause less pain or distress. In addition to this, the housing and day-to-day care of experimental animals can often be improved. Environmental enrichment—i.e. the provision of resources that enable animals to interact with, and control, features of their environment, and to engage in motivated behaviours—normally improves animal well-being (e.g. Olsson & Dahlborn 2002; Wolfer et al. 2004). In some experiments, appropriate anaesthesia and analgesia can play a vital role in pain management (e.g. Morton 2007).

Where animals are experimentally required to develop a progressively severe condition, as happens in degenerative disease models, an important refinement can be achieved by humane endpoints. In this sort of case, the technician or researcher uses clinical signs as endpoint parameters rather than awaiting the animal's spontaneous death. Interestingly, housing adaptations and humane endpoints are also scientific considerations; severely affected animals not offered the refinements are likely to die from secondary causes (for example dehydration or malnutrition in rodents unable to feed and drink from the cage top), rather than the disease under study. Survival/mortality when the cause of death is unknown, or only indirectly related to the disease, is not a high-quality variable to measure. As demonstrated by Scott and colleagues (2008), failure to consider non-disease-related mortality in a neurodegenerative disease model may even account for false treatment effects.

How to Maintain Standards?

In previous sections of the chapter, we have tried to describe, and explain the theoretical basis of, a range of ethical norms and standards applying to laboratory animal use. In this final section, we turn to look at how these standards are maintained. The maintenance of standards in society is invariably achieved through a combination of 'hard' regulation and 'soft' promotion. People are encouraged to act in ways society deems acceptable both by rules (sometimes backed by sanctions), and by policies that promote a positive attitude to the values underlying those rules.

Though we focus mainly on regulation below, we do not underestimate the importance of the soft promotion of responsible attitudes to animal research. Nobody imagines for a moment that sexism, for example, can be eradicated from society through legislation and regulations alone. We know that policies reinforcing anti-sexist culture and values are also required. Similarly, it is impossible to ensure that animal-based research is ethical simply by imposing rules and regulations. Ultimately, the aim must be an animal research community identifying with the values that underpin the rules—to create and maintain a culture, within animal experimentation, of ethical responsibility.

With that important proviso, we turn now to regulation. Who is responsible for ensuring that animals are treated ethically in the laboratory, and how well do they do their job? The first part of this question is much easier to answer than the second. Most animal-based research is funded,

directly or indirectly, by public money. This means that the public, or society as a whole, must be counted among a research institution's stakeholders. Society uses a number of mechanisms to guarantee that research on animals is carried out in an acceptable way. The most obvious of these is legislation, which in terms of enforcement is a powerful tool. But the legislative process is sluggish, while science and technology develop rapidly, and this means that laws must be broadly drafted if they are not promptly to go out of date.

As a consequence, the real decision-making on treatment of animals in research projects is usually delegated to an ethics, or animal care and use, committee. Committees can act in a more flexible way. They are also able to enter into dialogue with scientists proposing experimental projects and in that way, challenge scientists to develop their research in line with evolving best practice. Ethics committees and other similar bodies are often the only formal regulatory bodies tasked with looking in detail at research projects. A complete and transparent review process is dependent on committee composition and dynamics; it should represent all important stakeholders in the discussion equally. There seem to be at least three main stakeholders:

- researchers / industry (usually represented by scientists) that have an interest in being able to perform their proposed studies,
- animals (usually represented by veterinarians and animal care-takers) that have an interest in being protected from harm, and
- society (represented by lay members as well as interest groups, such as patient organizations and animal protection organizations).

The involvement of a wide range of parties with various approaches to the ethical issues raised by animal research will help to reduce the risk of committees becoming biased toward researchers —a risk that has been noted in at least one study (Schuppli & Fraser, 2007).

Not every aspect of animal research can be under the ethics committee's control, and the ultimate responsibility for the way animals are used rests with individual researchers. This is true, not just in moral terms, but also practically, as many decisions with ethical implications are made in the course of ongoing research. It can therefore be argued that critical discussion and self-regulation within the scientific community is hugely important. Those actually performing animal-based research must ask *themselves* whether their work prompts ethical concerns. The earlier sections of this chapter are intended to assist with that kind of enquiry.

Increasingly, ethics and the 3Rs are considered in the assessment of funding applications. In the review of manuscripts submitted for publication, by contrast, it seems that most journals continue to require merely a statement affirming that the research complies with official recommendations, relevant legislation, and/or an ethics committee's decision. It would be hard to deny that scientific journals could make better use of their position in the research process to raise the ethical standards of animal use. Refusals to publish papers based on the ethics of methodology would send a very strong signal to scientists. A policy of encouraging, or requiring, the authors of papers containing

animal-based research to describe any ethical problems raised by their work would also be beneficial. It is noticeable that information on the adverse effects of experimental methods on animals is rarely reported in scientific papers (e.g., Olsson et al 2008).

Finally, society has a legitimate interest in the activities of animal researchers. This is not only because much research involves public money, but also because sentient animals are a type of being deemed worthy of consideration and protection. This means that scientists using animals are, at some level, accountable to society; they must seek to explain their work, and they must seek equally to listen to public concerns. Engagement of this kind is always in the scientist's best interests. As we remarked in the previous edition of this chapter, in the twenty-first century, transparency and accountability are watchwords, applied in most areas of collective human endeavour. Thus, faced with questions about their work, the worst thing animal researchers can do is try to shut the enquirer out (Olsson et al. 2002).

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